Liver Circulation and Function during Isoflurane and Halothane Anesthesia

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Hepatic arterial blood flow (HABF) and portal blood flow (PBF) were measured in 18 dogs while awake and during isoflurane and halothane anesthesia. Surgical preparation 1 week before the measurements consisted of a left thoracotomy, placement of a left atrial catheter, and insertion of another catheter into the distal aorta via the left femoral artery. Cardiac output and liver blood flow were determined using microspheres at three stages: stage 1—awake state; stage 2—after 45 min of 1 MAC of isoflurane (eight dogs) or halothane (10 dogs) anesthesia; and stage 3—after 45 min of 2 MAC of inhalation anesthesia. Half-life and fractional clearance for indocyanine green (ICG) were determined 1 day before the experiment (awake state), and at the end of stages 2 and 3. Mean arterial pressure (MAP) and cardiac index (CI), as well as PBF, decreased during isoflurane and halothane anesthesia. HABF increased significantly during isoflurane anesthesia, remained unchanged during 1 MAC of halothane anesthesia, and significantly decreased during 2 MAC of halothane anesthesia. Apparently, hepatic oxygen supply was maintained much better during isoflurane than during halothane anesthesia. PBF correlated with CI during halothane (r = 0.97) and, to a certain extent, with MAP during isoflurane (r = 0.86). HABF correlated with CI and MAP during halothane (r = 0.74 and 0.71, respectively) but did not correlate with systemic hemodynamic variables during isoflurane. ICG half-life significantly increased during 1 and 2 MAC of halothane anesthesia. The degree of increase did not correlate with the level of anesthesia or the decrease in total hepatic blood flow. Isoflurane anesthesia was not accompanied by significant changes in ICG half-life. The data suggest that halothane has a more deleterious effect on liver blood flow than does isoflurane and, in addition, interferes with liver cell ability to absorb and excrete ICG. (Key words: Anesthetics, volatile: halothane; isoflurane. Liver: blood flow; function. Toxicity: hepatic.)

STUDIES CONCERNED with anesthesia-induced hepatotoxicity in rats indicate that halothane is more destructive to the liver than isoflurane.1,2 The difference may be explained by the reductive metabolism of halothane3,4 or by a more pronounced liver hypoxia during halothane than isoflurane.1,5 Halothane anesthesia is accompanied by a significant retention of bromsulphalein (BSP) on the first postanesthetic day, while such retention has not been observed after isoflurane anesthesia.6 The increase in BSP retention may be related to the decrease in liver cell function or to a decrease in total hepatic blood flow (THBF) with a concomitant decrease in delivery of the dye to the liver. Equimolar doses of halothane and isoflurane might lead to different degrees of respiratory and systemic or regional circulatory depression.

THBF determines clearance of drugs with a high hepatic extraction.7 It appears, though, that oxygen supply to the liver depends more on hepatic arterial blood flow (HABF) than portal blood flow (PBF). Calculations show that if HABF is 20% of THBF, the hepatic arterial blood contributes 27% of hepatic oxygen uptake; if the arterial flow proportion is 30%, the arterial blood contributes 65% of the oxygen consumed.8 It is clear that the ratio of HABF to PBF might play a more important role in liver oxygen supply than changes in THBF per se. For this reason, HABF and PBF were measured during isoflurane and halothane anesthesia and compared with awake values.

This study addresses two hypotheses: 1) that isoflurane and halothane may cause different types and/or degrees of liver circulatory disturbances; 2) that changes in hepatic clearance of indocyanine green (ICG) may be associated with changes in THBF.

Methods

The study was performed on 18 mongrel dogs weighing 15–20 kg. Surgical preparation was performed under pentobarbital anesthesia (30 mg·kg⁻¹ iv) and controlled ventilation. The preparation required a left thoracotomy, placement of a left atrial catheter, and insertion of another catheter into the distal aorta via the left femoral artery. The ends of the catheters were externalized into a specially designed pocket on the dogs' back. The dogs were allowed to recover for 1 week. During this time, the animals were taken into the laboratory every day for environmental conditioning and flushing of all catheters. Two days prior to the experiment, 100–120 ml of blood were taken from the dog for blood replacement during the main experiment. Blood volume was replaced with 350–400 ml of lactated Ringer's solution. One day prior to the main experiment, indocyanine green (ICG) was injected in a dose of 5 mg·kg⁻¹ iv and eight blood samples were collected for ICG concentration determinations at 2, 3, 5, 8, 15, 20, 25 min after injection. The ICG concentration was measured using the photometric method. Half-life (t₁/₂) of ICG was determined from the plot of ICG concentration vs time. Fractional clearance of ICG (in ml·min⁻¹) also was calculated using the least-squares model.9

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The day following the ICG test, the catheters were connected to transducers, and left atrial and systemic arterial pressures were measured. Arterial blood gas tensions and pH were measured using an instrumentation laboratory (IL) 813/pH blood gas analyzer; oxygen content was determined with an IL 282 CO-Oximeter. After 20 min of stabilization, the first set of microspheres was injected into the left atrium for cardiac output and liver blood flow determinations (stage 1—awake state). Following the first injection of microspheres, anesthesia was induced with sodium methohexital (4 mg·kg⁻¹), endotracheal intubation was performed, and inhalation anesthesia was begun. The desired end-expired concentration of anesthetic (1 MAC) was achieved within 10 min (first 5 min inspired concentration equaled 2–3 MAC) and maintained for 45 min. End-expired concentrations of 1.4% for isoflurane (eight dogs) and 0.9% for halothane (10 dogs), both in oxygen, were considered as 1 MAC. Methohexital was chosen for induction because of its shorter half-life than sodium thiopental. At the end of 45 min of inhalation anesthesia, the second set of microspheres was injected into the left atrium (stage 2—1 MAC of anesthesia). The ICG test was repeated exactly the same way it was done before the main experiment. Blood volume was replaced with blood that had been collected 2 days before the experiment. Then, the end-expired concentration of the inhalational agent was doubled within 10 min and continued for another 45 min. At the end of this stage (stage 3—2 MAC of inhalation anesthesia), a third set of microspheres was injected into the left atrium, which was followed by another ICG test.

End-expired concentration of isoflurane was monitored with the Enström Gas Analyzer® (EMMA). With a minimum 30-min warm-up period, the EMMA was zeroed against room air. A humidity-retaining device, "artificial nose," separated the EMMA sensor from expired humidified air. Water vapor values consistently showed 0.5 vol%; therefore, the actual value of end-expired isoflurane or halothane concentration equaled a read-off value minus 0.5 vol%. Thirty random EMMA measurements were compared with measurements obtained with the Perkin–Elmer Medical Gas Analyzer® (mass spectrometer), Model 1100, and the values were found to be identical. Controlled ventilation was provided during the second and third stages of the experiment. The animals were ventilated with an Air-Shield® respirator to maintain PaCO₂ at 35–40 mmHg. Rectal temperature was monitored and kept at 38°C by electrical heating pads.

At each stage, 1.2–1.8 × 10⁶ microspheres of 15 ± 1.5 (SD) μm in diameter were injected into the left atrium to measure cardiac output and liver blood flow. Reference blood samples were collected from the distal aorta at a constant rate of 10 ml·min⁻¹ for 3 min starting 10 s prior to microsphere injection. The microspheres were labeled with ⁸⁵⁴⁷⁷⁸⁷⁰⁸⁹⁴⁰⁴¹⁴²⁴³⁴⁴⁴⁵⁴⁶⁴⁷⁴⁸⁴⁹⁵⁰⁵¹⁵²⁵³⁵⁴⁵⁵⁵⁶⁵⁷⁵⁸⁵⁹⁶⁰⁶¹⁶²⁶³⁶⁴⁶⁵⁶⁶⁶⁷⁶⁸⁶⁹⁷⁰⁷¹⁷²⁷³⁷⁴⁷⁵⁷⁶⁷⁷⁸⁷⁹⁸₀⁰⁰∞ g⁻¹. The microspheres were injected into the left atrium immediately after the mixture was shaken vigorously for 2 min on a Vortex® mixer. The injection of spheres was made over a period of 30 s, followed by an additional 20 ml normal saline at body temperature. After the third set of microspheres was injected and the third ICG test performed, the heart was arrested with intravenous potassium chloride. The kidneys and splanchnic organs were removed for dissection, activity counting, and blood flow calculations. Activity found in the liver was used for HABF calculations, while activity in all other splanchnic organs was used to calculate PBF.

The radioactivity in the tissue and blood samples was analyzed with a Tracer® 2250 gamma counting system (Tracer Northern, Middleton, WI) which utilizes the least-squares fitting technique to resolve the amount of radioactivity contributed by each isotope in gamma ray spectra obtained by NaI detector for individual tissue and blood samples. This method employs an isotope calibration file that contains the decay rate, number of counts per microsphere, and the spectral definition of each isotope used in the study. Once loaded into memory, this calibration file was used by the microsphere analysis program (MSA) to conduct a comparison of the spectra contained in the file (standard spectra) and the determining spectra of the blood or tissue sample. The MSA program calculated the blood flow per gram of tissue and cardiac output. The experiment was disregarded if the difference in blood flow through the cortex of the left and right kidney was greater than 15%, since greater values were considered indicative of inadequate mixing of microspheres in the bloodstream.

Statistical analysis system (SAS) was used for all statistical computations. Data analysis consisted of correlation variables at each stage. The overall test of differences in response variables between groups and stages was done by repeated measurements in time analysis of variance model. Correlations between flows, pressures, and ICG test variables in the overall stages in each animal were calculated by linear regression technique. Homogeneity of slopes between animals was tested. For those responses in which the slopes were found to be homogeneous, the common slope for all animals was calculated. The r is reported as the measure of correlation.
Results

Changes in cardiac index (CI), mean arterial pressure (MAP), liver circulatory variables, and ICG test are summarized in Table 1. Left atrial pressure values did not change significantly during either isoflurane or halothane anesthesia. MAP and CI decreased during 2 MAC of isoflurane and halothane anesthesia (Table 1). PBF decreased during 1 and 2 MAC of both inhalational anesthetics (Table 1, fig. 1). HABF increased significantly during isoflurane anesthesia, remained unchanged during 1 MAC of halothane, and significantly decreased during 2 MAC of halothane anesthesia. THBF decreased during halothane and did not change significantly during isoflurane anesthesia. The arterial fraction of THBF increased significantly at 1 MAC of both isoflurane and halothane anesthesia, remained high at 2 MAC of isoflurane anesthesia, and returned toward baseline values during 2 MAC of halothane anesthesia. The arterial fraction of THBF was significantly higher at 2 MAC of isoflurane than at 2 MAC of halothane anesthesia (Table 1).

ICG pharmacokinetics fit a one-compartment model with a relatively low volume of distribution (0.25 ± 0.01 l·kg⁻¹). ICG half-life significantly increased during 1 and 2 MAC of halothane anesthesia. The degree of increase in half-life was not dose dependent. Isoflurane anesthesia was not accompanied by significant changes in ICG half-life. Alterations in calculated fractional clearance mimicked the changes in ICG half-life: Fractional clearance decreased during halothane anesthesia and did not change significantly during isoflurane anesthesia.

Correlations were found between systemic and hepatic circulatory variables (Table 2). THBF was correlated strongly with CI and MAP during halothane anesthesia. This association was not found during isoflurane anesthesia. Reductions in PBF were associated strongly with decreases in CI and MAP (although to a lesser extent) during halothane anesthesia. During isoflurane anesthesia, reductions in PBF were not associated with changes in CI but were related to decreases in MAP. Changes in HABF correlated with changes in CI and MAP during halothane anesthesia but not during isoflurane anesthesia.

Table 1. Liver Circulation and Function during Halothane and Isoflurane Anesthesia (Mean ± SE)

<table>
<thead>
<tr>
<th></th>
<th>Awake</th>
<th>1 MAC</th>
<th>2 MAC</th>
<th>Awake</th>
<th>1 MAC</th>
<th>2 MAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI (l·min⁻¹·m⁻²)</td>
<td>3.57 ± 0.36</td>
<td>3.53 ± 0.40</td>
<td>2.33 ± 0.50*†</td>
<td>4.17 ± 0.45</td>
<td>3.53 ± 0.61</td>
<td>2.33 ± 0.49*</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>111 ± 8</td>
<td>100 ± 5</td>
<td>64 ± 6*†</td>
<td>107 ± 6</td>
<td>97 ± 8</td>
<td>74 ± 7*</td>
</tr>
<tr>
<td>HABF (ml·min⁻¹·g⁻¹)</td>
<td>0.218 ± 0.048</td>
<td>0.430 ± 0.060*</td>
<td>0.395 ± 0.057*‡</td>
<td>0.322 ± 0.090</td>
<td>0.364 ± 0.076</td>
<td>0.173 ± 0.053*‡</td>
</tr>
<tr>
<td>PBF (ml·min⁻¹·g⁻¹)</td>
<td>1.281 ± 0.192</td>
<td>0.943 ± 0.121*</td>
<td>0.742 ± 0.211*</td>
<td>1.091 ± 0.131</td>
<td>0.621 ± 0.103*</td>
<td>0.502 ± 0.104*</td>
</tr>
<tr>
<td>THBF (ml·min⁻¹·g⁻¹)</td>
<td>1.461 ± 0.401</td>
<td>1.389 ± 0.223</td>
<td>1.125 ± 0.252</td>
<td>1.365 ± 0.281</td>
<td>0.957 ± 0.163*</td>
<td>0.625 ± 0.188*</td>
</tr>
<tr>
<td>HABF/THBF</td>
<td>0.19 ± 0.02</td>
<td>0.32 ± 0.09*</td>
<td>0.35 ± 0.05*‡</td>
<td>0.21 ± 0.03</td>
<td>0.38 ± 0.07*</td>
<td>0.29 ± 0.02‡</td>
</tr>
<tr>
<td>ICG t½ (min)</td>
<td>12.2 ± 1.4</td>
<td>13.0 ± 1.6</td>
<td>15.5 ± 2.2</td>
<td>11.2 ± 1.2</td>
<td>17.2 ± 2.2*</td>
<td>16.6 ± 2.1*</td>
</tr>
<tr>
<td>Fractional CI (ml·min⁻¹)</td>
<td>0.504 ± 0.065</td>
<td>0.476 ± 0.045</td>
<td>0.390 ± 0.062</td>
<td>0.554 ± 0.068</td>
<td>0.387 ± 0.066*</td>
<td>0.363 ± 0.058*</td>
</tr>
</tbody>
</table>

CI = cardiac index; MAP = mean arterial pressure; HABF, PBF, and THBF = hepatic arterial blood flow, portal blood flow, total hepatic blood flow, respectively; ICG t½ = half life of Indocyanine Green; Fractional CI = fractional clearance.

* P < 0.05 versus control in corresponding anesthetic.
† P < 0.05 versus 1 MAC in corresponding anesthetic.
‡ P < 0.05 isoflurane versus halothane in corresponding stages.
Table 2. Correlations between Systemic and Hepatic Circulatory Variables during Isoflurane and Halothane Anesthesia

<table>
<thead>
<tr>
<th></th>
<th>Isoflurane</th>
<th>MAP</th>
<th>Halothane</th>
<th>MAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>HABF</td>
<td>$r$</td>
<td>$P$</td>
<td>$r$</td>
<td>$P$</td>
</tr>
<tr>
<td>PBF</td>
<td>0.53</td>
<td>0.18</td>
<td>0.66</td>
<td>0.015*</td>
</tr>
<tr>
<td>THBF</td>
<td>0.53</td>
<td>0.22</td>
<td>0.66</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

CI = cardiac index in $\text{mL/min} \cdot \text{m}^{-2}$; MAP = mean arterial pressure in mmHg; HABF = PBF, and THBF = hepatic arterial blood flow, portal blood flow, total hepatic blood flow, respectively, in $\text{mL/min} \cdot \text{g}^{-2}$; $r$ = correlation coefficient; $P$ = significance level.

* $P < 0.05$ with F test control in corresponding anesthetic.

Discussion

In previous studies, PBF and THBF consistently have been found to be decreased during halothane anesthesia.\textsuperscript{16-24} In contrast, the reported changes in HABF during halothane anesthesia have varied tremendously in different studies. In studies where laparotomy was performed and/or barbiturate anesthesia was used as the control state, HABF usually decreased.\textsuperscript{16-21} On the other hand, in experiments where methods did not employ laparotomy or baseline barbiturate anesthesia, HABF was increased or unchanged, provided blood pressure and/or cardiac output were maintained within 70% of control.\textsuperscript{22-24} The discrepancy between studies, with and without laparotomy, is apparent due to the fact that laparotomy per se evokes splanchnic circulatory disturbances.\textsuperscript{25} A decrease in PBF is one of the disorders that by itself leads to an increase in HABF.\textsuperscript{26,27} Barbiturate anesthesia also might increase HABF\textsuperscript{28,29}, therefore, halothane given later would decrease HABF from already increased levels. In this case, a normalization of flow would be misinterpreted as a reduction. Information related to the changes in liver circulation during isoflurane anesthesia is very limited. One study demonstrated a reduction in PBF and a statistically insignificant although rather substantial—82% and 47%—increase in HABF during 1.45% and 2.18% of isoflurane anesthesia, respectively, in pigs.\textsuperscript{30}

In our study, PBF decreased during both halothane and isoflurane anesthesia. Under normal conditions, the PBF is strongly dependent on cardiac output.\textsuperscript{31} Apparently, this relationship is preserved during halothane anesthesia and somehow disturbed during isoflurane anesthesia (table 2).

Changes in HABF were different during halothane and isoflurane anesthesia: HABF substantially increased during 1 MAC of isoflurane anesthesia and remained at control level during 1 MAC of halothane anesthesia. During anesthesia at 2 MAC, HABF still was increased during isoflurane and substantially decreased during halothane anesthesia. An increase in HABF can be related in part to a reduction in PBF. It is well known that any decrease in PBF usually is accompanied by an increase in HABF.\textsuperscript{26,27} This increase is probably compensatory in nature in order to maintain the oxygen supply to the liver. Our data showed that the ability of hepatic arterial vasculature to increase (or at least to maintain) blood flow was lost during 2 MAC of halothane anesthesia. Conversely, following 2 MAC of isoflurane anesthesia, HABF substantially increased, despite reduced MAP and CI. Two hypotheses are suggested: HABF increase is a compensatory mechanism for the reduction in PBF, thus, demonstrating preservation of hepatic autoregulation. Alternatively, presuming a loss of autoregulation, isoflurane directly dilates the hepatic arterial vascular bed independent of changes in CI, MAP, or PBF.

THBF is the essential factor in the pharmacokinetics of drugs with high hepatic extraction.\textsuperscript{7} However, oxygen supply to the liver may depend more on HABF than PBF.\textsuperscript{8} Both halothane and isoflurane decrease PBF equally. HABF was increased with isoflurane, therefore, $O_2$ supply to the liver is greater with isoflurane than halothane. The enhanced supply side of the supply/demand ratio with isoflurane suggests an increased oxygenation. However, the relative decrease in metabolic demand between the two agents remains unknown. Consequently, the apparent advantage with isoflurane remains conjectural.

Changes in ICG half-life and fractional clearance did not correlate with changes in liver blood flow. An increase in ICG half-life might result not only from a decrease in THBF but also from a decrease in the ability of the liver cells to absorb the dye. The difference in action of 1 and 2 MAC of halothane on cardiovascular function can be striking, while it might be noticeable in terms of effect on the ability of the liver to absorb ICG. Thus, halothane not only decreases THBF but may adversely affect liver function at the cellular level, while isoflurane does so to a much lesser extent or does not affect cell function at all.

In conclusion, it appears that our first hypothesis is confirmed: Isoflurane and halothane do cause different types and degrees of liver circulatory disturbances.
disturbances are such that hepatic oxygen supply is maintained much better during isoflurane than during halothane anesthesia. PBF appears to depend almost exclusively on cardiac output during halothane anesthesia and, to a certain extent, on MAP during isoflurane anesthesia. HABF correlates with cardiac output and MAP during halothane anesthesia but not during isoflurane anesthesia. The second hypothesis is rejected: Changes in ICG test are not associated with a decrease in THBF, which probably means that halothane (but apparently not isoflurane) interferes with liver cell ability to absorb and excrete the dye. The test cannot be used as a method for THBF determination during inhalation anesthesia.

References